at close to 90 percent of those patients with abnormal imaging findings doing rather well thirty years later.

The indication is that whatever type of physiologic stressors that caused the changes arthritically may well be self-limited. The question becomes, do we need to do a surgical procedure to get the same results long-term that the support therapy does.

We don't really know, thirty years, if that is the case unless I have not seen that literature from Dr. Christensen or a longitudinal cohort of patients over thirty years exists. That would be an important thing to see.

DR. HEFFEZ: Dr. Christensen, do you wish to address the panel?

DR. CHRISTENSEN: I think of many cases. But I go back to the very first one I operated. And this is not against what you are saying, Richard, but this is the lady that had a meniscectomy. Then she had a condylectomy and she ended up with a fibrous ankylosis.

She was going down hill. There was no way that she was going to get any better. Putting in that implant in there, forty years later, she has--other than I finally had to put in a condyle on one side, but the other side, thirty-eight years, a year later than that first, I did a fossa-eminence implant for a perforation, she has never had another surgery there.

So if you add up those two sides, I have got about eighty years history on that one patient. She wasn't doing that well when she had a meniscectomy. She got three or four years before she began to fuse up again. I have seen many like that, plus a lot of our SLA models. I could show you one after another of these things fusing up, where they have taken the disc out and done meniscectomies, and we have to go into a total-joint--many, many of them. Some of them don't.

DR. HEFFEZ: Dr. Patters?

DR. PATTERS: Mark Patters. Dr. Heffez, I think the panel is struggling here because it is very difficult to deal with these questions that FDA has posed without first dealing with the overriding question as to whether this is an approvable PMA and whether there is the existence of satisfactory valid scientific data to be reasonably assured of safety and effectiveness.

All of these questions, as I see them, look at possible indications of which indications are proven or not proven, but I don't really know that we can answer this question without having some feeling where the panel stands on the overriding issue of the PMA, itself.

So I am suggesting that we are going in circles and, without dealing with the PMA, itself, and whether it is approvable, can we, then, look at what indications may be

appropriate and what are not.

DR. HEFFEZ: I agree with you, but I have found that sometimes if we go through the questions and we are raising certain questions, it helps come to that--answer that question. So if we can go to question 4 and then question 5, and then--

DR. BESSER: Can we stop at question 3 on the way?

DR. HEFFEZ: Sure. We were on question 3. Let me just finish my point. Once we finish doing that, we will return and ask that global question. It might bring us some data. Dr. Besser?

DR. BESSER: Dr. Besser. Back to question 3, one of the contraindications. There was a vague statement in one of the physician things about excluding patients with high loads, or susceptible to high joint loads. I would like that quantified. Current data supports loads up to about 50 pounds, so if there are patients whose disease or presentation would cause them to load the joint at greater than 50 pounds, I would consider them contraindicated.

DR. STEPHENS: How would we know that? How would we get that information?

DR. HEFFEZ: Dr. Stephens has a question. Repeat the question again.

DR. STEPHENS: The question is how would we get that information?

DR. BESSER: Dr. Besser. I am not sure that people have done either modeling studies of the TM joint or have actually instrumented the TM joint to look at what forces at the TM joint are normal or with certain activities.

I know that, in one of the findings, I think it was from the FDA, they printed the normal forces of the joint were 80 pounds for chewing, I think, and up to 300 pounds for clenching of teeth. I am not sure if that was at the tooth interface or at the joint. Perhaps, someone can give an indication for this.

DR. HEFFEZ: Dr. Christensen?

DR. CHRISTENSEN: I think we are the only company in the nation or the world that has done a so-called kinematic study of a normal joint, a partial fossa-eminence joint and a total joint of our system on fifteen subjects and came up with the figures.

And then we had that backed up by another study done at Clemson University, where I happen to be on the faculty at the Engineering School, on that, too. The total-joint patient is only generating about 20 pounds or less of force in that joint. The partial joint is going up to 35 to 45.

We don't see these 300-pound bites and all this stuff. We measured it with transducers and fluoroscopy and

everything that goes with it, and all the scientific and engineering data that goes with it, and you are not seeing that kind of thing in this type of patient.

So when you are trying to start limiting, then you put that alongside of our clinical experience, I have not seen a total joint fall apart, or a partial joint fall apart because of that type of pressure. I have seen a few of them where they have been hit in motor accidents or somebody has come in with a sledgehammer and hit them and that does change things a little bit.

But, in the overall thing, the science is there that this thing does stand up to the pressure that we expect in that joint.

DR. BESSER: Dr. Besser. Then I am wondering why, in the Physician's Guide, in your submission, you have a phrase here; "Those patients which create abnormal forces within the joint need to be alerted to possible injury or fracture of the prosthesis due to increased force placed on the implant."

DR. CHRISTENSEN: We did that to help compromise and satisfy the FDA.

DR. BESSER: It leads me to the question of how big is too big.

DR. CHRISTENSEN: We measured it. So, since we have measured it, we know that these things fit in that

area. If they don't, you go to a custom implant. If you have some big-jowled individual with acromegaly or something else, you can go to a custom implant and fortify the whole thing more than that if you need to.

But we have not seen that happen. So, to try and restrict Dr. Urbanek and Curry and all these other doctors and say, "You can't do this on a patient that might have some weird pressure," gets to be a bit academic.

DR. HEFFEZ: Dr. Hewlett?

DR. HEWLETT: Ed Hewlett. Dr. Christensen, is it, then, your contention that all of the incidences in the clinical situation of fractured fossa-eminence implants have occurred through means other than the shear biting force of the patient?

DR. CHRISTENSEN: They have occurred--I don't recall anything that I think fits into the shear biting force of the patient. I have seen doctors, and I have done it, myself, in years past, try to bend the fossa-eminence implant in a pair of pliers and crack it or break it. We warn against things like that.

But there have been a few cases where they have been in motor-vehicle accidents, where they have been hit. There has been a case or two where somebody--and this was in years before--somebody kept cranking the jaw open when bone grew up around this thing and they should have gone in and

taken out the bone around it.

If you crank it enough, you are going to break something. You either break right through the base of the skull, you break the jaw, or you break the implant. I have seen other motor-vehicle accidents where the jaw breaks and the implant stays intact. So you have got a number of things to think about.

DR. BESSER: Just to follow up, the study that you quoted from Clemson, is that included in here somewhere?

DR. CHRISTENSEN: Yes. It is in the PMA.

DR. BESSER: You wouldn't know where, would you?

DR. CHRISTENSEN: No; I don't. Brian May--when I was a reviewer on the program.

DR. HEFFEZ: Dr. Curry?

DR. CURRY: Dr. Curry from Denver. I would like to respond, and I don't know who asked the question about have we ever seen biting force cause a fracture of the Fossa-Eminence Prosthesis. I think the only Fossa-Eminence Prostheses that have been reported fractured were combined as a total joint prosthesis.

I have never heard of, and personally never seen, a Fossa-Eminence Prosthesis fracture in clinical use as a partial joint replacement.

MR. ALBRECHT: May I make one comment, Dr. Heffez?

DR. HEFFEZ: Yes.

MR. ALBRECHT: Doug Albrecht, TMJ Implants. In the clinical report that the panel was given, page 26, we do have a summary of our NDRs and it does refer to fractures of the Fossa-Eminence Prosthesis and we would like to review that.

DR. HEFFEZ: I would like to go to question 4 so we can get some global understanding of this PMA and then revisit the questions. Question 4, this partial joint prosthesis, the Fossa-Eminence Prosthesis, is designed to articulate on the natural condyle, mandibular condyle, which raises concern regarding the potential for degeneration of the natural condyle.

The first question, do the engineering data, based on the total joint prosthesis, provide adequate support for use of the Fossa-Eminence Prosthesis as a partial joint prosthesis? If not, what additional data is necessary? Are the inferences in the engineering data, basically, from the total joint adequate to be applied to the Fossa-Eminence Prosthesis?

How do people feel about that?

DR. ANSETH: Kristi Anseth. I think, in part, a bulk of the data that represents just the basic material properties, biocompatability, are very similar for the two joints and show a reasonable degree of safety of the material, itself. I think there is still a little bit of

the issue of the load that is experienced, which we just talked about, whether there should be any restrictions on that.

And then, related to part 2 of this question, from the non-clinical data, there really is no engineering evidence about the metal-to-bone that I thought supported that it would not cause degeneration. So I thought there was lack of evidence from that perspective.

The clinical data, again, the N is very small. So there is a little bit of uncertainty in terms of what we are looking at, but there is some clinical evidence that there is not as much degeneration. But, from my perspective, that information is lacking.

DR. HEFFEZ: So the second part of the question is, do the engineering and clinical data demonstrate that the metal-to-bone articulation will not cause degeneration to the natural mandibular condyle, and you feel that there is not enough data to support--

DR. ANSETH: I don't believe there is enough evidence--the engineering data, I don't think, supports that. The clinical, I will defer to some comments from the clinicians.

DR. HEFFEZ: Dr. Cochran?

DR. COCHRAN: As regards the clinical data, we saw some nice radiographs that showed that there was not much

condylar change. But I feel like, a little bit, we are going down the path that endosseous dental implants went down where the data you are looking at or the cases that have been successful and that you can follow.

Without prospective data, we don't know if the ones that are dropping out, the patients that are dropping out, maybe they are having problems in that area so I don't feel like we really have sufficient data and we won't have it until you do a prospective trial and follow the patients and look for changes on radiographs over time.

DR. HEFFEZ: How would you suggest evaluating the changes in the condyle? We already note there is some difficulty sometimes in evaluating it through CT. You are relying mostly--in most cases, it would relying on linear or polytomograms or panoramic radiographs.

DR. COCHRAN: I acknowledge the fact that it is not an easy thing to measure, but I would like to see some sort of measure of that in a prospective fashion, be it on whatever radiograph you could find. But it would be on all the patients and not only on the patients that are just successfully treated.

DR. HEFFEZ: In a qualitative fashion, in other words.

DR. COCHRAN: Some sort of qualitative--whatever you can do.

MR. ALBRECHT: May I respond, please?

DR. HEFFEZ: Who said that? Yes.

MR. ALBRECHT: Doug Albrecht, TMJ Implants. That is part of the prospective study. We do collect radiographs, panorex radiographs, on all patients at every follow-up visit. It will be evaluated at the conclusion of the study.

DR. HEFFEZ: How are you evaluating them? What is the scale that you use to evaluate the changes on the radiographs?

MR. ALBRECHT: We don't have a scale. We are going to have them reviewed by a radiologist and provide the results at that point.

DR. HEFFEZ: My suggestion is that you should have a well-defined scale.

MR. ALBRECHT: I am sure the radiologist has a scale of disease process that he looks for when he does examine these. I am not familiar with that type of scale but they will be evaluated.

DR. HEFFEZ: Okay.

DR. BERTRAND: Peter Bertrand, question.

DR. HEFFEZ: Can you wait one moment, Dr. Bertrand? Does somebody from industry want to--

DR. CHRISTENSEN: I would like to answer that in another way. You know, Dr. Urbanek, back here, has had 351

partial joints out there going back ten years, or whatever the number is. Any of us that are clinicians in here realize particularly that, if you have a bilateral or a unilateral in which that condyle is shrinking away, that jaw tends to move that direction.

That jaw tends to slide and you get an anterior bit. You don't have to be a rocket scientist in radiology--I am not saying that we don't do that, but you don't have to be a rocket scientist in radiology to determine these condyles are not melting away.

Otherwise, this occlusion is not staying there. I am sure you are just as familiar with that as I am. I know Dr. Curry and Dr. Urbanek both can speak very well to it.

DR. LIPPINCOTT: I am Al Lippincott. I am the bioengineer consultant to TMJ implants. I don't have any financial obligation to the company. But, to answer your question, Dr. Anseth, about any studies that have been done of the metal against bone, there are three articles that I am aware of in the orthopedic literature where they have done animal studies regarding cobalt chrome as one of the materials.

But, in many cases in the orthopedic literature, they are also evaluating cartilage degeneration as well. So whether it would be in reference to actual bone that you would see in the TM joint, that is what would have to be

reviewed.

DR. HEFFEZ: I think Dr. Bertrand had a question, initially.

DR. BERTRAND: If we are trying to three-dimensionalize whether there is loss of condylar formation, and these patients have CAT scans, why not three-dimensionalize the CAT scan, make a model down the line, take another CAT scan and three-dimensionalize it, and compare over time. That technology is readily available now.

DR. HEFFEZ: Dr. Hewlett?

DR. HEWLETT: Actually, I would like to pose a question to, is it Dr. Lippincott? In your manuscript of your wear study that was included in the materials, you described a gross examination of three explanted polymethylmethacrylate condyles and described visible to the naked eye wear on those condyles.

One, I believe it had been in for eleven years, went to extent that the plastic had worn away down to the metal core that serves to hold the polymethylmethacrylate in place. Albeit it is a very small sample of these, I found it somewhat interesting in that, in this entire body of information, it is the only example of two dissimilar materials functioning in vivo in the TMJ implant situation.

I would be interested to hear your opinion on how

the wear of the polymethylmethacrylate might be extrapolated towards our concerns about the wear, understanding, of course, that polymethylmethacrylate can't regenerate itself.

But I guess my ultimate question is is there possibly a subset of patients out there whose regenerative capability might be exceeded by some abrasive wear that would occur between the bone and the fossa-eminence implant.

DR. LIPPINCOTT: Al Lippincott, to answer your question. Understand that in those retrieved devices, we did not see any foreign-body reaction, or none was reported. In many cases, we didn't receive any histology sections of tissue to identify that, but identification by the surgeon, there was no inflammatory reaction. I wanted to make that clear with the methylmethacrylate.

Granted, there is more extensive wear regarding the comparison of bone against cobalt chrome. All you can take is, really, the clinical data and what you are seeing. In many cases, if there was a retrieval or there was a need to go back into that joint, my understanding, from the clinical side, they didn't see any staining of the tissue that would make one think that there was wear from the fossa component as far as identifying where, from bony erosion of the bone.

Again, it all depends if histologies were taken. Really, even that would be subjective as to whether you

could identify that or not.

DR. HEFFEZ: Dr. Besser did you have a question?

DR. BESSER: I wanted to--sorry; doing three things at once.

DR. HEFFEZ: Dr. Curry?

DR. CURRY: Jim Curry from Denver. I don't know of a clinician that is doing this type of surgery that is not also somewhat concerned about the response of the natural mandibular condyle of our patients to the use of an alloplast in the joint. We are all concerned about that.

My approach to this, a little bit, has been I don't know of a test that you can do preclinical to help us with that understanding because, as you well know, if you put a splint on a patient for any length of time, you are likely to get some changes, radiographically, in a mandibular condyle with no surgery at all.

Or, in the case that I showed earlier, if a patient goes through standard other kinds of surgery, the entire condyle may fall away and melt away. And so we don't have any real understanding of what the process is that makes progression of disease. To blame it on the Fossa-Eminence Prosthesis, when we have, literally, thousands of patients out there that we can look at clinically.

If the natural mandibular condyle was going to wear away because of the metal, it ought to be happening

most of the time. You may find an occasional case where, as you have suggested, there may be some odd-ball physiological reason why that patient it didn't happen to. But the majority of patients ought to have that condyle melting away in front of our eyes and I am telling you that simply is not happening.

It doesn't happen with anybody that I know that uses this. And we all follow our patients both clinically and radiographically.

DR. COCHRAN: This is David Cochran. I don't think the intention of the question was that we were blaming the implant. It was simply that the only way to determine if there is a relationship or an association with success or, in fact, you can prove that there is no change is to do it prospectively and look in the different patient groups, the ones that are successful and the ones that are not successful, and show whatever changes occur.

It is just going to document the changes. It is not saying that necessarily there is something wrong. But you have got to do the study. You have got to do the prospective study and follow all the patients and make that determination. It is the only way you are going to do it.

DR. CURRY: Dr. Curry from Denver. In response to that, I agree with that. But I also agree that there is some validity to retrospective analysis looking at people

who have been around for ten or fifteen years that we have access to. You may not have a presurgical CT scan on a patient that has been out there ten or fifteen years.

We didn't know to do it then. But we can get some of those patients, and that is what I tried to do, and look at what their condyles look like and what their bite looks like and what their clinical picture looks like and extrapolate from that what is going on.

DR. COCHRAN: I agree with you, but I think you are missing the point. The point is the cohort that was followed longitudinally, where you have it, are the ones that have been successful. The interesting group is the ones that were not successful and to show that maybe there weren't bone changes in that group either.

That is the group that is most interesting. Then you have got a comparison and you have got an association.

DR. CURRY: Dr. Curry from Denver. I think I understand your point but, as a clinician, I see various kinds of patients who have varying degrees of disease in their joints and I have not ever been able to correlate one specific treatment to bringing on a more rapid progression of disease except in the case of teflon and proplast, which I did very few of, and silastic.

I have seen those joints melt away within just a few months. And so we made a natural correlation to that

and we are having to do the same thing with this prosthesis.

MR. ALBRECHT: Doug Albrecht, TMJ Implants. One other way to look at it is in our cross-section data, of the 1270 patients for which we did have clinical data on preoperatively, and I grant you, yes, some of those patients are not followed up totally out to the five years, but I did look at all 1270 patients.

We would know if they progressed from a partial joint to a total joint because we would have to supply them with the total joint. Out of 1270 patients, only 25 patients have progressed to a total joint from a partial joint. If I do the math right, that is less than 1 percent.

That pretty much is for either iatrogenic placement, infection, loose screws. Unfortunately, in 19 cases, the physician did not provide us any information why they went from partial to total. But, still, it is less than 1 percent out of all those patients with partial joints that have progressed, for some reason or another.

DR. HEFFEZ: Dr. Besser?

DR. BESSER: Mark Besser. I found the reference in the original PMA for the TMJ joint loads. They are a little bit higher than what Dr. Christensen had stated. He stated it for, if you will pardon the expression, the normal group. Average values were 388 Newtons. That is about 75 pound. The maximum value for a subject was 621 Newtons,

130, 140 pounds.

The lower values given for the Fossa-Eminence only in the total TMJ groups were 200 Newtons, about 50 pounds, and 91 Newtons for the total joint group. But, again, even for the Fossa-Eminence group, the maximum value for a subject in that group was 536 Newtons, about 120 pounds.

Therefore, my concern still stands when looking at this population as to whether a contraindication for people with high TMJ joint loads exists and whether some determination of that joint load--and this modeling was done from a bite load through some anatomical modeling to get a joint load.

So it is possible that minimum values for bite load, or maximum values for bite load, should be determined and used as a criteria for acceptability of this prosthesis.

DR. CHRISTENSEN: This is a good point. But you have to take into consideration about 10,000 fossa-eminence implants out there in people, maybe 11,000. Half, or a certain figure of that, maybe 4,000 or 5,000, are total joints. The rest of them are partial joints. Out of all of that, as Dr. Curry said, I don't know that I remember anybody fracturing that fossa in the normal situation.

Am I wrong?

DR. HEFFEZ: Thank you, Dr. Christensen.

DR. BESSER: Dr. Besser. To follow up, I think

that--I agree with what you are saying and understand what you are pointing out. I am answering the question that was asked of me, which talked about the engineering data. I think there is a 30-year history of clinical data that cannot be ignored, especially when looking at some of the questions we have been asked about condylar-joint degeneration where it is very difficult to simulate in a lab, and you can't ignore the fact that you have an awful lot of data from the clinic that may make working very hard to simulate it in the lab unnecessary or irrelevant.

However, I am concerned by some of the engineering data that has been presented, looking at it as an engineer, and would like to see additional data.

DR. LIPPINCOTT: May I comment on that?

DR. HEFFEZ: Identify yourself.

DR. LIPPINCOTT: Al Lippincott from TMJ Implants. I understand, and it was identified by FDA, that the metal-on-metal represented the worst-case condition which represented point contact. Understand, with point contact, you have higher stresses.

If we talk about only a hemiarthroplasty only with bone with a broader surface onto the implant surface, your contact stresses will be substantially reduced.

DR. BESSER: I am assuming that the loading that was put in here for the normal group assumed bone-on-bone

interface if you have a better model or, I guess, a better method for measuring what that joint contact force is. When we are looking at fatigue and the wear values and the wear data that was generated was using a bearing force of 35 pounds, the fatigue data, again, using 130 pounds, I believe.

It would be nice to look at that at a higher force and see what additional wear or what the fatigue behavior of the prosthesis was.

DR. LIPPINCOTT: Al Lippincott, again. Just a comment on that, as well. We did look at much higher loads under a static condition. Really, understanding fatigue and its relationship to a static load, usually, it is, of course, a lower percentage that you will see as far as failure.

Basically, what we did, as well, is after fatiguing the device, we did a static load to failure and found that, even at the static load, we were at much higher forces, I think around the 650 pound, something like that.

DR. BESSER: Mark Besser. I have no problem with the static loads that you subjected this to and its yield strength. We have no argument there.

DR. HEFFEZ: I would like to move on. Question 5, I think, has been answered, really. We have been discussing if there are safety concerns, what measures can be taken to

mitigate these concerns. We discussed loading. Were there any other safety concerns that panel members had?

DR. BERTRAND: Peter Bertrand. Are we sure the quality-control modifications pointed out by the FDA, that the metallurgic problems are satisfied?

DR. HEFFEZ: Are we sure we have to rely--is that a question to me?

DR. BERTRAND: Sure; to anybody. There were some difficulties that the FDA had with interpreting whether the gas-carbide problem--they have made suggestions. My understanding is that those suggestions have been undertaken, but have the suggestions shown that, yes, the problem is indeed taken care of.

I am not aware that we know that it has been taken care of. Or am I misinterpreting?

DR. HEFFEZ: I believe Ms. Angela Blackwell--if you would like to come to the microphone just to clarify what you said before regarding the gas porosities in carbides.

MS. BLACKWELL: The questions about the carbides have not been answered specifically yet. There is a procedure in place to answer them. They can't be answered until the company is back into production. They don't have anything to test.

DR. HEFFEZ: Dr. Besser?

DR. BESSER: Mark Besser. Are there criteria in place, once they are back into production and they have something to decide whether it passes or fails?

DR. HEFFEZ: Does industry want to reply to that question?

MR. DURNELL: This is John Durnell. Yes; quality-control measures are in place once normal production has resumed.

DR. HEFFEZ: Is this information that you feel is proprietary and that you don't wish to reveal at this meeting with the people present?

MR. DURNELL: Proprietary.

DR. HEFFEZ: Dr. Besser, do you feel that you want to hear this information? We would arrange for that.

DR. BESSER: No; Ms. Blackwell has indicated that the criteria were in place for success and failure when they go back into production and I am comfortable with that. Thank you.

DR. HEFFEZ: Yes?

MR. LARSON: Floyd Larson. I was just looking at that section. It is in binder 3, if you have it handy there. That section, or at least the FDA comments regarding that section, are addressed in binder 3 but it is not paginated.

DR. BESSER: About how far in?

MR. LARSON: I only have a section of it scanned in here. I think it is near the front. It could even be about page 7.

DR. HEFFEZ: Any other questions? Comments?

MR. ALBRECHT: Doug Albrecht, TMJ Implants. May I respond to Dr. Burton's question early on regarding the registry not being a study and the prospective study being a study?

DR. HEFFEZ: Fine.

MR. ALBRECHT: I agree with you. It is not a controlled clinical study. But, for preamendment devices, again, the FDA has said it could be a prospectively controlled study, case histories or significant human experience. We believe that the registry is significant human experience. We are looking at thousands of patients, to begin with and, granted, the follow up is not ideal--

DR. HEFFEZ: I think Mr. Ulatowski indicated already that we should be using all data available including the registry.

MR. ALBRECHT: Okay.

DR. HEFFEZ: I would like to, at this time, move to the open public hearing.

Open Public Hearing

DR. HEFFEZ: Since we had an extended open public hearing in the morning, I would like to only reduce this to

a total of fifteen minutes. If there are people that would like to address this panel, please identify yourself and we will bring you to the podium.

MS. LUCAS: Ellen Lucas. I have no financial anything. I was just listening here about a few people have had this, and very few people have had that. I must be very special because I was looking at some of my op reports and I have had--since I had the all-metal joint in, I had ankylosis on both the left and the right, and loose screws. And then--let's see, heterotopic bone on the right and metallosis and staining on the left.

So I have had all these different things in just two surgeries, they were discovered. That was since the metal joint was put in.

Thank you.

DR. HEFFEZ: Dr. Patters?

DR. PATTERS: Question for Ms. Lucas, if I could.

MS. LUCAS: Excuse me. I also forgot my pathology report that states I also had a giant-cell reaction.

DR. PATTERS: Mark Patters. If I could ask a question of you. One of the overriding concerns is the number of patients lost-to-follow-up. You have had a negative reaction. Was that reported by your implanting doctor to--in other words, are you one of the people lost-to-follow-up or are you in the data?

MS. LUCAS: I sent MedWatch forms in to FDA and I also tried to call the company but I never got a response.

DR. PATTERS: But did your implanting surgeon report to--

MS. LUCAS: I don't know that for sure. I don't know.

DR. PATTERS: So you could be someone lost-to-follow-up?

MS. LUCAS: I could be lost; yes.

DR. PATTERS: Thank you.

MS. LUCAS: Thank you.

DR. HEFFEZ: Is there anybody else who wishes to address the panel in the open public hearing? Ms. Cowley?

MS. COWLEY: Terrie Cowley with the TMJ Association. Just one thing which hits very hard to a patient listening to a learning curve of twelve patients and learning TMJ by trial by fire. All I could think of was what was the condition of those twelve patients while this person learned how to do the procedure.

Another. Dr. Christensen is extremely proud of his fifty years of dealing with this joint. I kind of wish we had fifty-years worth of data on the screens today. I have not heard one mention of the immunological--not immunological, per se, but the allergic reaction to materials that we are hearing increasingly from the

patients.

Another person talked about things happened in two months and then everything seems to be fine. I am talking to people who have broken devices in their heads now for three years. Their surgeon either will not take it out, they are waiting for something else, or they just don't want to get into surgery No. 22.

So whether it has happened in two years, whether it has happened in four, the devices are out there breaking. I feel compelled to reaffirm what I mentioned this morning and that is that this panel, should you choose to approve any of these devices, you must include in the labeling that an independently monitored TMJ Implant registry be established complete with the explanted device analysis and input from the patients.

Thank you.

MS. HOSFORD: Toni Hosford. I just wanted to say that you tend to hear, as far as for follow up, more complaints than people who are doing well with their implant. People that are doing well generally go on their merry way and they don't have any reason to go back to the doctor and complain.

I also believe that if the correct surgery is done in the first place, then there is no need for other surgeries. I have had no other surgeries, no allergic

reactions, did all the conservative methods. I do believe in this product. I sympathize with people that have had multiple surgeries, but I do think, regarding data, it is hard for doctors to keep track of patients that are happy and don't come back.

It does take time to call the patients and try and talk them in to coming back to get an X-ray to see how they are doing.

Thank you.

MS. COWLEY: Is it possible for me to address the panel?

DR. HEFFEZ: Yes; you may.

MS. COWLEY: Terrie Cowley, TMJ. We hear this an awful lot from all different treating professionals, the splinters, the grinders, and so forth. All of these patients are doing so terrifically. My question is, without scientific data, how can you ethically subject a patient to either getting better or turning out so horrendously as the over 10,000 people who have called us?

DR. HEFFEZ: Anybody else wish to address in the open public hearing?

We are not going to have the break. We are going to move along and do the open committee discussion at this time.

Open Committee Discussion and Vote

DR. HEFFEZ: At this point in time, I would like to bring up Dr. Patters' point. If you could reiterate your point.

DR. PATTERS: Mark Patters--my point regarding dealing with the issues of safety and efficacy before we look at indications?

DR. HEFFEZ: Correct.

DR. PATTERS: Yes. I feel that we have to come to grips with whether, as defined by the law, that there is reasonable assurance of safety and efficacy based upon valid scientific data and deal with that issue. Once the committee has established its point of view, then to determine what possible indications or contraindications exist.

So I would recommend that is where the discussion be focussed.

DR. HEFFEZ: At this point in time, I think it would be valuable to have Pamela Scott read out a definition of safety and a definition of effectiveness. We have it on a powerpoint slide.

MS. SCOTT: The definition of safety, and the reference for this is 21 CFR 860.7, section (d), subsection (1). "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health under the

conditions of use outweigh any probable risk. The valid scientific evidence shall adequately demonstrate the absence of unreasonable risk associated with use of the device under the conditions of use."

The definition for effectiveness; again, 21 CFR 860.7, section (e), subsection (1). "There is a reasonable assurance that a device is effective when, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when labeled, will provide clinically significant results."

DR. HEFFEZ: Thank you, Ms. Scott.

So, let's address the first issue of safety. I would like to hear from the committee whether they feel that there is enough scientific evidence including all the evidence that has been provided, including the registry.

MS. MORRIS: Could I make a comment?

DR. HEFFEZ: Yes.

MS. MORRIS: Lynn Morris. I am the consumer representative on the panel. I find today's discussion very difficult. On one hand, if I were a patient or a member of my family or a loved one had the pain and chronic conditions that TMJ causes, I would definitely be desperately seeking Dr. Christensen's or Dr. Urbanek's phone number to help me.

On the other hand, although I don't have any technical ability to assess the data here, I am concerned

that--I know that the FDA is now looking at the least burdensome way to prove something. But I am concerned that the panel still has a responsibility to have the data in front of them to make the decision on safety and efficacy, and to make that decision based on scientific data, not on any data that is presented, either here or that you specifically know otherwise.

The other issue that concerns me is that it seems like, perhaps, you are using the registry as part of that decision. I guess I would like to be assured that you consider that scientific data because it doesn't appear, from my experience, to be that. That is one issue.

The other is while I don't have any experience on the technical end of this, I do have experience in the regulation of medical professions. When I walk away from an FDA meeting as a consumer representative, I want to be very assured that the product is clinically proven to be safe and effective, because if I have to rely on the learning curve of practitioners, which I see every day, I would be very nervous.

So I guess, basically, my two concerns are that we really have the scientific data to show it is safe and effective and that we take concern and really look at what the learning curve is and, if we are going to go forward with this, what we are going to require.

DR. HEFFEZ: If I may ask you a question. As a consumer, I would interpret it as saying that you would not want to see any device being used from a preventive point of view--in other words, to prevent more serious disease from occurring--is that correct? If I interpret what you are saying, you would rather have a device available as a salvage procedure.

MS. MORRIS: No; I am not saying that. Again, I think that that issue is more practice-related. I guess, just from a comfort level, and I think you talked earlier about the panel having a comfort level with safety and efficacy, because I am somewhat less comfortable with the practice end of it--I mean, the surgeons and the doctors that are here today are very distinguished, and I would put myself or my loved ones in their hands.

But I have seen many, many surgeons in the regulation of medical practice that I would feel much less comfortable with. So, starting out, I want to be really assured--and I think the consumers in the audience do as well--that the device really has a pretty significant level of safety and efficacy.

For me, that would be to have a good deal of scientific data to show that. I guess that comfort level has to be higher when there is a learning curve involved. The higher the learning curve, the more you would want to

see--at least I would want to see on the safety and efficacy side.

DR. HEFFEZ: Thank you. Dr. Patters?

DR. PATTERS: Mark Patters. I have some serious concerns about using the registry data for safety because it requires an assumption be made about the patients that are not represented in the data. We know that the sponsor presented data of 1358 cases and, at one year, there were only 555 available.

So, nearly 60 percent were lost-to-follow-up. To know whether their device is safe, I would have to know something about those 60 percent. One can argue that the most successful patients don't return to follow up. One can also argue that those who feel that they have been damaged don't return for follow up.

I don't know the answer, but I find the prospective study is the place where safety data should emerge that should be clear. Unfortunately, at this point, the prospective study is not far enough along to make any conclusions from, at least conclusions out to 24 and 36 months.

So I have some concern that the data is not available at this point, but should be available in future, to answer questions about safety.

DR. HEFFEZ: Do you feel the prospective study, as

it is constructed, is adequate--will be adequate to answer those questions?

DR. PATTERS: I don't know that, but I know that the prospective study is a protocol which requires, to fulfill the protocol, that follow-up examinations be done on patients and patients know that entering the study. That is far different from the registry data which relied on whether implanting surgeons returned forms and were able to contact patients.

So, certainly, as designed, if 60 or 70 percent of the patients can be retained in the study, it should provide that answer.

DR. HEFFEZ: But the study, as is constructed with inclusion criteria, exclusion criteria, those, you feel, would, once the study is completed, be able to answer those questions in your mind.

DR. PATTERS: With the caveat of being able to retain the majority of patients out to 36 months.

DR. HEFFEZ: Dr. Burton?

DR. BURTON: Dr. Heffez, and this is probably to Dr. Patters as well, and Dr. Janosky who has addressed these issues, too, I think that it probably is adequately constructed. The question is going to be, given the current input numbers that exist, whether the 36-month point, particularly in some of these subcategories which have

extremely small numbers, whether we are going to have enough to have a reasonable correlation with those.

I guess the question, then, is the clinical trial correctly designed. The answer to that may be yes. The question is, is it large enough that, at 36 months, we are going to have an adequate number of patients and a significant percentage of the patients, enough to make a decision based upon that.

DR. HEFFEZ: Dr. Hewlett?

DR. HEWLETT: One suggestion for the structure, the construction of the prospective study, in spite of the overwhelming empirical evidence, as Dr. Curry pointed out, that the fossa-eminence implant does not result in degenerative damage through abrasion to the natural condyle. I would urge for inclusion in the protocol of some standardization, probably in the radiographic follow up, that would facilitate, as close as we can get, to a quantitative assessment of changes in the condyle over time.

I would urge that some modification of this nature be added to the protocol to settle, once and for all, this question of condylar changes, if any, in the partial implant situation.

DR. HEFFEZ: Dr. Cochran?

DR. COCHRAN: I would reinforce what Dr. Hewlett has said. Any time you design a prospective trial, you

should set the outcome variables in advance. In this case, I would use a blinded radiological assessment tool of some sort to make that.

My point I wanted to make was that, given the current design of the prospective trial, I am a little worried that, a year from now or two years from now or whenever it comes back to this panel, given the inclusion criteria without better definition, we are going to still be struggling with the same questions about which patients can be operated, how many had ankylosis, how many had prior alloplast, and if that number is still 3 percent or 4 or 5 percent, I just worry about what kind of conclusion you are going to be able to make for that particular indication.

DR. HEFFEZ: So if I had to summarize, the current protocol could be improved by looking back at the inclusion criteria, consolidating, defining them a little bit better, that we could look at establishing standard means of evaluating radiographs, define clear what the adverse effects are; for example, device-related, meaning implant loosening versus screw loosening. They are both in both different categories. Define better unanticipated chronic pain, for example.

In other words, provide a better, more objective means of evaluating the results that would improve the current protocol.

The reason why those items are brought up is to be efficient and provide a less cumbersome way of evaluating everything, we do wish to find an answer to these questions and we don't want to keep asking the same questions over and over again.

Other comments from committee members? Yes?

MS. WARMON: Sue Warmon, patient representative. As a recovered TMJ patient, I would be extremely hard-pressed to bring a member of my family to face one of these procedures without some type of long-term study that would give me the information on the safety and the effectiveness of this product.

I don't think three years is enough to satisfy me. However, I do recognize the fact that there are TMJ patients out there who will grasp at anything to relieve their problems. I recently read an article in a local paper of a woman who had twelve separate surgeries and still was having problems.

So you have to understand that a TMJ patient, when faced with the tremendous pain and disability that they live with every day will go to any means and any doctor who promises to give them some relief.

I would hate to see these patients end up in the hands of someone who didn't have the skills to use this product compounded with no longitudinal data to support it.

DR. HEFFEZ: As a consumer, though, would you--I am trying to be as objective as possible--as a consumer who would be in tremendous pain, seeking some avenue of resolving your pain, do you think it is appropriate, at that time, to undergo an operation with a device that may not have the scientific background that you would like to have?

MS. WARMON: That is a real hard situation to answer. I know when I was faced with my surgery, there was a long process of thought that went into it before I agreed to it. I have no implants. I think I would really want to know what the long-term effect of something foreign in my body would be. I think I would look at other means before I would do that.

MS. MORRIS: Could I please answer the same question. Lynn Morris. I am the consumer representative. I truly understand that question and it is a struggle. It is a struggle in my mind, particularly after hearing everything today. But I think we need to be incredibly aware of the panel's responsibility.

As I understand it, and please correct me if I am wrong, it is not the panel's responsibility to do this balance that we are seeking. It is the panel's responsibility to insure safety and efficacy with scientific data.

DR. HEFFEZ: You are correct in knowing what the

panel's goal is, but we have to evaluate everything in a very objective fashion and ask all the questions that we feel are related to the issue at hand.

Other questions?

MR. ALBRECHT: Doug Albrecht, TMJ Implants. I would like to respond to the comments regarding the size of the studies and the validity of the studies that we presented, or the validity of the data that we presented.

As I stated before, for preamendment devices, the FDA has given us the opportunity to provide significant human experience as well as any controlled clinical trials and any case histories presented by physicians. I believe we have done that.

In our registry, granted, the follow up is not ideal, but if you look at the numbers that are in each follow-up period and the number of devices and number of patients, we are looking at 1300 partial-joint patients in almost 2000 devices, that we have available some data out to five years.

I can't imagine that all these patients are the good patients and we have not seen any of the bad patients. I am sure there is a mix in there. I cannot separate them out at this point. Regardless, the numbers speak for themselves. Out to 24 months, we have 286 patients reporting a pain level of 2.1. At 36 months, we have 166

patients reporting a pain level of 1.9.

We are doing the prospective study and we are correlating that with what we have seen, given us an idea of what we would expect to see in a prospective study. So we are doing the prospective study. We correlate that with what we see in the registry right now and the numbers are pretty much identical.

You overlay the grafts and the data, one on top of the other, they are almost exactly the same. Granted, we don't have the numbers long-term yet, but it would show me that the same trends are occurring. We may not have reached statistical significant, but I think there is clinical significance there that the device truly does work.

If we were to see some problems with the device, we would not see pain levels below 2.0 at three, four and five years from a group of 1900 patients.

Also, provided in the registry with regard to safety was our retrospective study in which we did look at safety issues, and we came up with only, out of over 300 patients, three device-relate issues that the physicians had indicated in that retrospective study.

If you look at our MDRs, we have less than a 0.2 percent MDR incident rate from every device that we manufacture. With regard to fossa fracture, we don't have any fractures from a partial joint alone. All fractures

were with total joints and most of them with trauma associated with the fracture.

So, with regard to the numbers; yes, I would agree with you. The numbers, long term, are not there yet. But if you look at all the data put together, I believe everything looked at together would provide reasonable assurance that the device is safe and effective at this point.

DR. HEFFEZ: I think the two biggest concerns that are coming out in the discussion are the evaluation of the failures and the longevity of the existing data in the prospective study. Those are the two issues, I think, that people are trying to grasp.

Dr. Patters?

DR. PATTERS: Two points. I may be mistaken, but in my previous experience on the panel, does not allow industry, the sponsor, at this point, to volunteer information when not sought by the chair. Am I wrong, Mr. Ulatowski, that this is a committee discussion?

MR. ULATOWSKI: That is correct. It is per the discretion of the chair to recognize any person at this time. But it primarily a panel discussion at this time.

DR. PATTERS: My second point is--

DR. HEFFEZ: I just want to say that I do feel that it is important, to try to come to an answer, to have

industry give that data.

DR. PATTERS: My second point is that I have no doubt that some patients have benefitted enormously from this device, but there appear to be some patients that have been injured by the device. I shouldn't say--they have been injured. Whether it is the device that injured them or the surgeon that injured them remains to be known.

But, certainly, we cannot discount that there are people here today who claim to have been injured. We really don't know as to what injured them. But that data needs to be available and I believe the prospective study has the best opportunity to provide it.

DR. HEFFEZ: Any other comments from the committee members? At this point in time, I would like to ask the sponsor to have an opportunity to make any final comments regarding the PMA. This will precede the voting regarding this PMA.

DR. CHRISTENSEN: I am not sure what else to comment about that we haven't commented about this time or last time. But, having been around surgery of this joint for fifty years, I can tell you that I know for sure this implant works. Some of you may not have that feeling, but I wish you could go into a surgery and watch these surgeons do it, and then watch these patients afterwards.

We don't see patients being reoperated as--I

forgot your name, but the person on the panel here that is a patient. I don't expect to. I didn't see it in my practice and I don't expect to see it in others providing it is done at the right time with the right disease.

So, having said that, we can try to compile data forever. We have got a lot of data. I don't know whether you have got it all. We have got an awful lot of data. I tell you--you may say, well, it is not structured just this way. Being an adjunct professor in bioengineering down at Clemson University, I know what studies are like.

But I also know that this is a preamendement device and if you look back at the hips and the knees, and so forth, some of them got through with 50 patients. One paper had no engineering. So I am saying that where we are, we have come a long way

I tell you, I am confident enough, myself, to have that implant put in me or my wife or my children--I have got ten children so I speak that with some trepidation--if that were the case. But I would have no problem putting this device in those children, or putting it in me.

MR. ROSEN: I am David Rosen. I am outside counsel to the company. I am also a former FDA employee. I just have a couple of other points I would like to make.

First of all, the prospective study is ongoing. It goes out to five years. The company has committed to

completing that study and to appropriately monitor that study and to comply with our reporting requirements. So the company will see any additional adverse-event data and is under an obligation to report such data to the agency under strict reporting requirements.

Second, there are procedures in place for the company to review explanted devices so they can see what is going on with the explants. And they have also made arrangements with physicians to look at the condylar portions of those bones, if they from a partial to a total. They can examine those if they go back into the joints, and the company would certainly commit to have procedures in place to look at the condyles when additional surgeries are going into that joint.

I think you have heard a significant number of the arguments with respect to the totality of the data that are here. It is consistent with the standards that this committee and that the agency has used in approving other TMJ implant types of devices.

I think if you look at the totality of the data that was used to approve a previous device that it would be consistent with the data that has been presented here today. Lastly, the company does have this ongoing obligation to monitor adverse events whether the products are through the registry. As they become aware of those types of things,

they have an obligation to investigate and to report those things if there is an increased trend in adverse device events or defects that are associated with the device.

Thank you.

DR. HEFFEZ: At this time, I will ask all industry representatives if they could leave that area. I would appreciate it.

I would like to ask if the industry representative has any comments on the panel regarding--Floyd?

MR. LARSON: Just one comment about the numbers. There is a lot of concern about the numbers, especially as the data are stratified. If you look at the protocol, the sample size that was calculated for the study was not based on stratification to those specific indications.

So question 2 is really dealing with indications that just were part of the "or" list of inclusion criteria. So, as I read the protocol, there wasn't any intention that each of those be indicated separately. So that is where the numbers look back when you look at them that way, but I think if you have a more general indication, obviously, the numbers still are not wonderful, but at least they are better than what they looked like when everything was stratified down so deeply.

That is just a comment on the protocol and on the numbers and how it relates to question 2 in particular.

DR. HEFFEZ: But regardless of whether they were stratified, they still had only data, really, up to six months, basically.

MR. LARSON: Right. It was about six months, was the 70 or 75 percent, not three months. Yes.

DR. HEFFEZ: At this time, I will ask Ms. Scott to read panel recommendations, options for the premarket approval applications.

MS. SCOTT: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act require that the Food and drug Administration obtain a recommendation from an outside expert advisory panel on designated medical device premarket approval applications that are filed with the agency.

The PMA, or premarket approval application, must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicably, publicly available, information. Safety, again, is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under the conditions of use outweigh any probable risk.

Effectiveness is defined as reasonable assurance that, in a significant portion of the population, the use of the device for its intended uses and conditions of use, when

labeled, will provide clinically significant results.

Your recommendation options for the vote are as follows; approval. Approval; there are no conditions attached. Agency action; if the agency agrees with the panel recommendation, an approval letter will be sent to the applicant. The second option for the vote is approval with conditions. Under this particular option, you may recommend that the PMA be found approvable subject to specified conditions such as resolution of clearly identified deficiencies which have been cited by you or by FDA staff.

Prior to voting, all of the conditions are discussed by the panel and listed by the panel chair. You may specify what type of follow up to the applicant's response to the conditions of your approvable recommendation you want; for example, FDA follow up or panel follow up. Panel follow up is usually done through homework assignments to the primary reviewers of the application or to other specified members of the panel. A formal discussion of the application at a future panel meeting is not usually held.

If you recommend postapproval requirements to be imposed as a condition of approval, then your recommendation should address the following points; the purpose of the requirement, the number of subjects to be evaluated, and the reports that should be required to be submitted. Agency action; if FDA agrees with the panel recommendation, an

"approvable with conditions" letter will be sent.

The third option is not approvable. Of the five reasons that the Act specifies for denial of approval, the following three reasons are applicable to panel deliberations. The data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling; reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling; and, lastly, based on a fair evaluation of all the material facts in your discussions, you believe the proposed labeling to be false or misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask that you identify the measures that you think are necessary for the application to be placed in an approvable form. Agency action; if FDA agrees with the panel's "not approvable recommendation," we will not send a "not approvable" letter. This is not a final agency action on the PMA.

The applicant has the opportunity to amend the PMA to supply the requested information. The panel recommendation will be reviewed by the panel at a future meeting unless the panel requests otherwise.

The last option is tabling. In rare

circumstances, the panel may decide to table an application. Tabling an application does not give specific guidance from the panel to FDA or the applicant, thereby creating ambiguity and delay in the process of the application. Therefore, we discourage tabling of an application.

The panel should consider a nonapprovable or approvable-with-conditions recommendation that gives clearly described corrective steps. If the panel does vote to table a PMA, the panel will be asked to describe which information is missing and what prevents an alternative recommendation.

Following the voting, the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. HEFFEZ: At this time, I would like to entertain a motion to proceed with the PMA. I am looking for a motion from the panel regarding this PMA. If one of the primary reviewers of this PMA--maybe they can assist us with a motion. Dr. Burton?

DR. BURTON: Richard Burton, University of Iowa. I move that it be placed in a not-approved status due to inconclusive safety and efficacy with the return to the company that, with completion of the existing IDE to completion with an adequate retention of the patient population would then allow return to the panel for approval.

DR. HEFFEZ: Any panel members wish to second this?

DR. BESSER: Mark Besser. I will second.

DR. HEFFEZ: Any further discussion? Dr. Patters?

DR. PATTERS: Question to FDA. I somehow missed, or failed to understand, why the device is off the market at present. Could you elaborate on that?

DR. HEFFEZ: Mr. Ulatowski?

MR. ULATOWSKI: Tim Ulatowski. Well, the term "off the market" isn't entirely accurate in a regulatory sense. The investigational program continues as a possibility for availability, albeit under investigational limitations. We have entertained, from time to time, requests for expansion of that investigation, given a firm justification and a good idea of what number of investigators are requested, and so on and so forth.

So it is certainly not commercially available because it is not approved, but the investigational program is still a viable situation with the product.

DR. PATTERS: Do I understand, then, it was withdrawn? It was commercially available and was withdrawn?

MR. ULATOWSKI: Once the PMAs were required, the product either had to be approved--when the 515(b) PMA requirement went into effect, you either had to have an IDE or some other authorization for distribution. So that is

the only authorization available for these products at this point in time until they are otherwise approved.

DR. PATTERS: Thank you.

DR. HEFFEZ: Any further discussion? Dr. Besser?

DR. BESSER: Mark Besser. In addition to the completion of the clinical trial, I would like to see some further preclinical testing, specifically fatigue analysis with a higher load; also, a more realistic, I guess, prosthesis underlying the substrate interface model, not the total contact embedded right now--I think it is some synthetic acrylic that was sort of embedded in so you had a total contact underneath the prosthesis.

But that is not, in fact, situation when the prosthesis is in the patient anchored with screws on the irregular substrate which was their former fossa.

DR. HEFFEZ: This is for both static and--

DR. BESSER: This is for the fatigue analysis and for the yield strength. I would like to see both of those. And some either retesting at higher loads or appropriate limitation as far as indications for use, especially since the data presented indicate that TMJ loads of 75 to 100 pounds are not uncommon, even if not the average for individuals with temporomandibular-joint disorder.

DR. HEFFEZ: Any other further discussion? Dr. Hewlett?

DR. HEWLETT: Edmond Hewlett. Just a little guidance from the chair, I guess. There are still remaining questions about the actual indications as far as how specific the indication of internal derangement should be. How should we address that? Is that addressed during discussion now or as an amendment to the motion?

DR. HEFFEZ: The PMA would be approved or disapproved. Under those circumstances, you would approve it but there would be certain conditions and we would then start talking about the specific indications and conditions. So that would be relevant if it was approved.

Am I right?

MR. ULATOWSKI: You are making a motion. I have heard a motion to disapprove. But you can't divorce the indications for use from your thought process here. You have made a motion, I suppose, and correct me if I am wrong, on the listing of indications in the data in hand. You can continue discussion along those lines and have an outcome.

However, you may also choose to come back to reconsider subsets of indications or other situations that may be more acceptable at this point in time in terms of the status of the product. So you have to consider what is given to you in the labeling.

DR. HEFFEZ: So I think it is best to revisit the motion by Dr. Burton and ask him to respecify his motion

whether the disapproval was for the indications as they were listed.

MS. SCOTT: Can I make a clarification just before we move on that the panel's recommendation is not approvable, just in terms of the regulatory sense, we are very sensitive to the actual language that is used. The panel's recommendation is not approvable and the agency makes the decision of agreement with that to either disapprove or to make another finding.

So the correct terminology would be not approvable in terms of the motion and in terms of the vote.

DR. BURTON: Richard Burton. I stand corrected. It is based upon the existing indications as they have been formulated and presented thus far which, obviously, includes internal derangement as one of the primary indications which, at least in the datasets that were presented to us, represented greater than 80 percent of the patients for whom it had been indicated and utilized.

DR. HEFFEZ: So, could you restate the whole motion?

DR. BURTON: I move a recommendation that it be disapprovable--

DR. HEFFEZ: Not approvable.

DR. BURTON: Not approvable; pardon me--not approvable based upon the lack of substantive safety and

efficacy data for the given surgical indications as seen currently in the PMA. It could be reconsidered for approval with the completion of the existing IDE to term with adequate retention of the dataset, the following of all explanted devices and further clarification of the surgical indication and to--sorry.

DR. HEFFEZ: The motion should just stand alone and then, after that, we can qualify the motion to see what industry could do to reach a higher level of--to get an approval status.

DR. BURTON: I'm very sorry. I will shorten it back to, be not approvable based upon the lack of adequate safety and efficacy data as presented.

DR. HEFFEZ: With the indications.

DR. BURTON: Yes; with the indications as presented in the PMA.

DR. HEFFEZ: Dr. Besser, do you still second that motion?

DR. BESSER: Yes; I still second that motion.

DR. HEFFEZ: Is there any further discussion? Mr. Larson?

MR. LARSON: Just a thought. Having been recovering from surgery at the time of the last meeting and, therefore, not being here for that meeting, I am not sure whether this is appropriate but should we consider whether

we are holding this device to a higher standard than has been done previously for similar devices, number one. Number two, are we being influenced substantially in terms of the interpretation of the clinical data by the very, very detailed list of indications and would both a less specific indication and maybe limitation to those III, IV and V, combined with a consideration of the level of support that has been required in the past, change our thinking on this?

DR. HEFFEZ: I think that, when we looked at the indications, we looked, basically, over approximately 80 percent was for one category; that was internal derangements.

MR. LARSON: If that was limited to III, IV and IV, you mean? Just III, IV and V?

DR. HEFFEZ: When we have understood the definition of inflammatory arthritis, meaning that that also included early internal derangements, it made it so fuzzy that, and correct me if I am not right, but the understanding was that this was referring to internal derangement, all categories. It wasn't clear.

MR. LARSON: Would clarification by industry help that situation? Would limitation, I guess, help that situation?

DR. HEFFEZ: I will ask Dr. Burton if he feels comfortable with his motion or whether he wishes to withdraw

it.

DR. BURTON: I still would feel that I am comfortable with the motion. I was present at the last meeting and I don't really feel that there is a change in standard from a clinical call of that. The reason that I feel that was that the other types of products that we have looked at have been oriented more toward a salvage or reconstructive approach whereas this, at least with the indications as they are currently presented, is indicated more as a first-line or an early treatment as opposed to the other.

Certainly, their support for that stems from the fact that they feel that that is an indicated type of procedure for the indications as--like I said, I guess I don't feel that there is a different standard because I think we are dealing with very, very different indications. My motion is based upon the indications as they have been presented and been followed within this PMA.

DR. HEFFEZ: Question?

MR. LARSON: I do understand that point and I guess I am thinking salvage as well. If the sponsor was willing to rather dramatically change that approach, would that make a difference in the recommendations of this panel in terms of that early-intervention attitude?

DR. BURTON: I guess that is a hypothetical case,

but I am not sure that we can really consider something that would be a relatively major change in what has been presented to us, consistently presented both in the last presentation, the last panel meeting, and what we have seen here thus far today.

MR. ULATOWSKI: Can I make a point?

DR. HEFFEZ: Yes. Mr. Ulatowski?

MR. ULATOWSKI: Mr. Ulatowski. I am looking at our voting expert in the audience. The question I would have is, with a nonapprovable on the table, considering the indications as listed, that is one sort of action. Another sort of action I seem to be hearing as an option or what other people may be thinking about is approvable, to entertain an approvable with the conditions of modifications to the labeling, or some such actions, which might be more amenable to some.

So we can consider both avenues, I suppose, but that is how I see it now.

MR. DEMIAN: Haney Demian. I am exec sec for the Orthopedic and Rehabilitation Devices Panel. I think that you would have to first vote on this particular motion or have him withdraw it. Then you could go to another main motion of approvable with conditions, and state your conditions, that the indications for use are a salvage procedure and not this first-line sort of prevention.

So it is really up to the person that made the motion either to withdraw it, and if he doesn't wish to withdraw it, since you already have a second on the table, you can vote that down and see if the votes carry.

If it does carry the not approvable, then you can state how the sponsor can place it into approvable form, meaning that they would have to narrow their indication for use down. Does that clarify it?

DR. HEFFEZ: Yes; thank you.

Any other discussion?

DR. BESSER: Mark Besser. Can I have a definition of "salvage?"

DR. HEFFEZ: I could provide a definition from a surgeon's point of view, simply that the patient is last resort basically, that the patient, perhaps, is in terrible pain, there are no other avenues to explore and the question is whether the patient has to remain in pain or whether you will salvage the case by performing an operation, with this device, not having all the--

DR. BESSER: I understand that part. I am wondering whether there are objective criteria for a patient who has exhausted all other options. I am uncomfortable with my level of understanding of what that would entail, approving this as a salvage device.

DR. HEFFEZ: Since we have a motion of the floor

and it has been seconded, we can deal with that issue following the voting of this motion. Okay? Mr. Ulatowski?

MR. ULATOWSKI: Looking back at the labeling for the Fossa-Eminence, I believe it is not labeled as a primary--if we could turn to that particular labeling, just make it clear to everyone.

DR. HEFFEZ: I will permit industry to make a brief statement to that effect, if you wish. Go to the podium, please.

DR. ROSEN: David Rosen. The indications statement, we have added a section to the warning which is bold. It says that, "This device is not intended as primary intervention in the case of internal derangement." That is in the proposed labeling that is front of the panel today. You can see we also have statements, "not responsive to other modalities of treatment."

In the design of this labeling, we were trying to fashion it as not being primary intervention, as being a salvage type of therapy. Thank you.

DR. HEFFEZ: Dr. Patters?

DR. PATTERS: Mark Patters. I would like to ask the chair to call the question. If this motion doesn't pass, then we can consider other options.

DR. HEFFEZ: I would call the question. I would like to go around the table for the vote. I would like to

start with voting members. Just to let everybody know, those voting members with be Dr. Anseth, Dr. Hewlett, Dr. Patters, Dr. Janosky, Dr. Bertrand, Dr. Burton, Dr. Stephens, Dr. Besser and Dr. Cochran. The chair will only vote to break a tie.

So I would like to go around the table starting with Dr. Besser.

DR. PATTERS: Just to clarify, we are voting on calling the question?

DR. HEFFEZ: Hold on just for one moment, please. One correction. Dr. Cochran is not available for vote. Dr. Besser?

DR. BESSER: The same question; we are voting on the motion to make it not approvable.

DR. HEFFEZ: That's correct, with the indications that are outlined.

DR. BESSER: I vote in favor of the motion.

DR. HEFFEZ: Following your vote, you can also state, at the same time, the reasons for that, if you can, Dr. Besser.

DR. BESSER: My reasons are as I stated earlier. I don't believe that the preclinical data adequately support safety and the clinical data, to date, also do not support safety and efficacy for the product yet.

DR. HEFFEZ: Dr. Bertrand?

DR. BERTRAND: Peter Bertrand. I vote not to approve based on the inclusions of internal derangements as part of the initial surgical procedures.

DR. HEFFEZ: So you vote in favor of the motion.

DR. BERTRAND: Right.

DR. HEFFEZ: Reasons? Would you like to state a reason?

DR. BERTRAND: I just stated the inclusion of internal derangements as an initial surgical procedure.

DR. HEFFEZ: Dr. Patters?

DR. PATTERS: I voted in favor of the motion and I feel it is not approvable at this time and that approval awaits completion of the prospective study.

DR. HEFFEZ: Dr. Janosky?

DR. JANOSKY: I am in agreement with the motion and the data for safety and effectiveness are insufficient at this time.

DR. HEFFEZ: Dr. Stephens?

DR. STEPHENS: Willie Stephens. I vote for the motion. I believe that the safety and efficacy of the procedure of the device has not been established at this time.

DR. HEFFEZ: Dr. Burton?

DR. BESSER: I vote in favor of the motion and, as the maker of the motion, I think my reason has been

previously stated.

DR. HEFFEZ: Dr. Hewlett?

DR. HEWLETT: I vote in favor of the motion citing inadequate safety and efficacy data from a controlled prospective trial.

DR. HEFFEZ: Dr. Anseth?

DR. ANSETH: I vote in favor of the motion, lack of substantive safety and efficacy data in the clinical set.

DR. HEFFEZ: As you know, if the recommendation is not approvable, then we need to identify some measures that we feel would be necessary to render this application approvable. So can we, at this time--we have mentioned a few and I am going to say them to be expedient. If there are others, or if you need to qualify what I say, please, committee members, feel free to speak up.

One item was that higher loads should be used in the fatigue analysis. Secondly, that there was some concern about testing for yield strength and fatigue analysis and the fact that the implant was placed against a substrate with multiple points of contact which may not correlate to the clinical situation.

We discussed the clinical device study protocol should clarify the inclusion criteria, clarify and define the inclusion criteria. It should clarify the specific radiographic means of evaluation of radiographs and should

clarify the definition of adverse outcomes.

I will ask the committee to identify any other measures that would help or assist in rendering this PMA approvable. I should add that the data that is coming from the prospective study should make every attempt to evaluate those failures and those patients who do not follow through with a complete examination.

Do I have any other measures that the committee members feel that should be included? Mr. Larson?

MR. LARSON: Only reflecting what I think I heard earlier, did I hear anything in this discussion just now about labeling, about indications?

DR. HEFFEZ: No.

MR. LARSON: I think that was one of the major issues as well, so I think that should be at least addressed.

DR. HEFFEZ: So we will add that the company should look carefully at the indications. The indications as they are stated seem to show some overlap, perhaps are poorly defined. If those can be more clearly defined, that would assist in rendering the PMA approvable.

Any other recommendations? Dr. Cochran?

DR. COCHRAN: Sort of as a follow up to that, we didn't hear anything, in the statistical review, about power analysis of any sort. I think if you are going to try to

clarify the indications, you are going to want to have some sort of statistical input as to power analysis for indications.

DR. HEFFEZ: Could you define better for us what you mean by power analysis?

DR. COCHRAN: I would refer to the statistician for that.

DR. JANOSKY: I have in front of me this clinical study protocol, TMJ96-001. My understanding is that that is the protocol that they have started and need to continue. If you look through there, the issue is presented in terms of sample-size estimation and most of those issues that we are talking about. So I don't know if the data were available and we just weren't given the data or it is just not collected yet.

DR. HEFFEZ: Okay. Any other measures that need to be identified? Dr. Hewlett?

DR. HEWLETT: If I could just clarify, I think, the comment about the evaluation radiographs. It was to the extent that it is standardized in such a manner to facilitate the monitoring of condyle changes over time.

DR. HEFFEZ: Correct. Any other comments? So the motion passes. Do we need to vote on the measures? No? Okay. At this point in time, I want to thank everyone for their input, both from industry and panel members, and ask

for a short break for ten minutes.

[Break.]

DR. HEFFEZ: We will ask Mr. Ulatowski to present on behalf of the FDA.

Discussion of Labeling for a Total Temporomandibular Joint

FDA Presentation

MR. ULATOWSKI: For closing today, we want to take just a few moments of your time, hopefully just a few moments, but that depends on you as much as me, for some comment, if any, on some aspects of the proposed labeling for the total joint, the metal-on-metal, total joint from TMJ Implants, Inc.

We are on a different track with the total joint. We are seeking only comments on labeling. Let me just preface by saying you heard some discussion this morning about the fatigue tests and the loading and the safety factors and the apparent low fatigue strength, perceived low fatigue strength.

We have a similar concern and we want to address that in the labeling for the total. We have been working with the company to provide some information for the surgeon to help him or her properly select patients for the total joint in view of the engineering data and results that we have.

[Slide.]

So if you examine just a couple of slides that I have in regard to those elements in the labeling that we have worked with them on, I would like to see if you have any other--or your reaction and any other comments to these in terms of contraindications as stated, the ability to exert significant postop masticatory muscle forces, or uncontrollable masticatory muscle hyperfunction, clenching or grinding, which may lead to overload and fracture of the device, or loosening of the screws.

This is a contraindication, a contraindication, for the total joint.

[Slide.]

Precautions; dynamic fatigue tests were conducted on the TMJ Implant's metal-on-metal total joint replacement system with the force applied vertically to the device. No failures occurred at or below 130 pounds. Physicians should carefully consider the results of these fatigue tests when considering patients with particular anatomical considerations or with high-normal to unusually high masticatory forces.

[Slide.]

We also had the inclusion of some not only observable adverse events during the course of the investigation but also those sorts of recurring adverse events that one may typically see in implant surgery. We

made suggestions regarding addition of those types of adverse events.

So, in brief, there you have it in regard to our response to the fatigue-test data and directions to the surgeon for proper selection and advice for selection of patients, given the fatigue-test results.

I ask simply if there are any comments or observations regarding what we have stated in the proposed labeling.

DR. BURTON: Richard Burton. Mr. Ulatowski, one thing I was not clear about before--

MR. ULATOWSKI: Angela and Susan; could you join me?

DR. BURTON: I'm sorry; what is the--both as labeling exists, what is the obligation of the implanting surgeon and the company in recording adverse events or explanation. I guess that is one of the questions we have had going along, is what happens to these and why does it seem that you get what certainly is anecdotal reports from various groups that are there but we don't ever see those.

So, is there any way within the labeling structure, or whatever, that we can have it set out--I can't say making it mandatory, but that that is somehow encouraged within that such that when adverse events or explanation might occur, that the mechanism is better defined?

MR. ULATOWSKI: I am open to suggestions but, under the investigational regulations, there are reporting expectations and those occurrences and observations are under tighter control during the investigational stage. Once a product is approved, made commercially available, there are physician and healthcare facility reporting requirements that are in place.

Do those requirements play out in terms of the types of reports we ought to be seeing? No. The reporting system is there but we don't often see all the reports that should have been submitted. That is a recurring deficiency with manufacturers and with the physicians.

So the mechanisms are there. To require additional reporting mechanisms I think is a bit overkill with this type of problem that you are describing.

DR. BURTON: Thank you. I am sure, actually, that most of the problem lies with the physician and not the company.

MR. ULATOWSKI: Yes; we can regulate up to the top of our head, require this and that. It doesn't necessarily mean people will execute those regulations as expected. We have not seen that execution as expected with all the regulations we have.

DR. BURTON: Thank you.

DR. HEFFEZ: Any other questions for Mr.

Ulatowski? Thank you very much.

MR. ULATOWSKI: Thank you.

DR. HEFFEZ: I would like to ask industry at this time to present.

Industry Presentation

DR. ROSEN: David Rosen on behalf of the company. All I want to say is that we worked very closely with the division to fashion this labeling. We believe that it is appropriate labeling. It conveys the right message. It is consistent with the labeling that is with the approved product. It is modeled directly after the labeling with the approve product and it is what we consider to be in the mode of salvage therapy.

So thank you.

Open Committee Discussion

DR. HEFFEZ: We are just going to take a two-minute respiratory break while I wait for Pam Scott to come back with some of the actual labeling documents because I don't feel that everybody has it in front of them; is that correct? So, if you would wait two minutes. If I could have one to read out to them.

You have had an opportunity to review this before. Are there any comments regarding it? One comment would be the use of the screws, only those screws for the system should be utilized. I am asking industry if they can--you

think on the Warnings, No. 4, if longer screws are necessary, do you feel that placing--in the document indicating specifically only those screws that come with the kit should be utilized.

My point is that there should be, in the Warning, that you should not use screws from other kits. I am saying that that should be inside the Warning.

MR. DURNELL: This is John Durnell. I believe it is in there.

DR. HEFFEZ: Is it located in the Warning Section? I don't believe so. Could you please come to the podium and identify yourself and then make your statement?

DR. CHRISTENSEN: Bob Christensen. That has been in the Physician Guide or the Package Insert for the past ten or twelve years so I am sure it hasn't moved. It will be in there somewhere.

DR. HEFFEZ: Yes; but my point is that is should appear under the Warnings.

DR. CHRISTENSEN: It will be under Warning, but maybe not in the thing you are looking at.

DR. HEFFEZ: It is located under Precautions. Any comments from the committee? Dr. Patters?

DR. PATTERS: Mark Patters. Does FDA want a motion here?

DR. HEFFEZ: Yes.

MR. ULATOWSKI: No.

DR. HEFFEZ: Oh; it is just discussion and comments.

MR. ULATOWSKI: Discussion and we are out of here.

DR. PATTERS: My comments are I strongly endorse the intended use as described in the document as negotiated between FDA and the sponsor.

DR. HEFFEZ: Any other comments from panel members?

DR. BESSER: Mark Besser. My only other comment has to do with the sort of nonspecified nature of uncontrollable masticatory muscle hyperfunction and then, later, when patients present with particular anatomical considerations are high-normal to unusually high masticatory forces.

I would ask whether clinicians at the table are able to ascertain this of their patients presurgery?

DR. HEFFEZ: The specific question is--

DR. BESSER: Is whether one can know presurgery whether someone has unusually high masticatory forces and how high is unusually high, what are those numbers? Are there any numbers on that at all, or is that just a clinical judgement.

DR. HEFFEZ: At this point in time, it is a clinical judgement. There is no routine testing of

masticatory muscle forces prior to placement of the implants, or devices.

Any other comments? With the failure to hear any other comments, I will move to closing comments. I would like to thank the members of the Food and Drug Administration, all the committee members, members from industry, many people who work behind the scenes whom I do not know their names, but without whom we would not be here.

I would specifically like to thank Ms. Scott, who has been very helpful in directing the meeting and keeping us on line. I hope that industry leaves here with some good recommendations so that, when it is brought again back to this panel, it will be easier to make it approvable, the PMA approvable.

At this point in time, I will turn the microphone to Ms. Pamela Scott.

MS. SCOTT: I would like to thank all of the panel members, consultants, representatives here today for attending the meeting and for your input into the issues at hand. I would like to thank you for your hard work.

I would also like to ask, just before we close, those who are voting members--Dr. Heffez, Dr. Anseth, Dr. Hewlett, Dr. Patters, Dr. Janosky--did I cover everyone? I am not sure if you all brought your calendars with you, because I was going to see if we could--maybe we can do it

by E-mail. I just want to see if there are particular dates that would be good to set up our tentative meeting dates for the Year 2001.

If you prefer, I can do it by contacting--okay; we will do it that way. Then, again, I would like to thank you for everyone's participation. I would like to thank all of FDA staff that was supportive for putting this meeting together. If there are no further comments, the meeting is adjourned.

[Whereupon, at 5:05 p.m., the meeting was adjourned.]

CERTIFICATE

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